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EXAMINER	
CANELLA, KAREN A	

ART UNIT	PAPER NUMBER
1642	29

DATE MAILED: 02/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/671,995	CHARI, RAVI V. J.	
	Examiner	Art Unit	
	Karen A Canella	1642	

-- The MAILING DATE of this communication appears on the cover sh t with the correspond nce address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *93-143* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *93-143* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 9, 2003 has been entered.

2. Please note that the examiner assigned to this application has changed.

3. Claims 1-92 have been canceled. Claims 93-143 have been added. Claims 121-136, drawn to non-elected method claims, are withdrawn from consideration. After review of the prosecution history, it is noted that the elected invention of a composition and kit had the further requirement of an election of species of a chemotherapeutic agent. Applicant elected paclitaxel (synonymous with taxol) as the chemotherapeutic agent along with the species of maytansinoid as an anti-mitotic agent, and the monoclonal antibody or a fragment thereof derived from N901 as the cell-binding agent in the paper filed February 14, 2002,. Newly added claims 93-120 are all drawn to maytansinoid as the anti-mitotic agent; the further requirement for an election of cell binding agent to be confined to humanized N901 or C424 is withdrawn. Accordingly, claims 93 and 120 will be examined to the extent that they read on the administration of paclitaxel as a chemotherapeutic agent.

4. Sections of Title 35, U.S. Code not found in this action can be found in a previous Office action.

5. Claim 120 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The recitation of "the" cancer cell in claim 120 lacks antecedent basis within the claim.

6. Claims 93-97, 99, 102-110, 112 and 115-120 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

As drawn to inadequate written description

Claims 93-97, 99, 102-110, 112 and 115-120 encompass pharmaceutical compositions and kits which contain a immunoconjugate comprising at least one maytansinoid compound linked to a monoclonal antibody or fragment thereof which binds to an antigen expressed by a cancer cell. Thus, the claims are dependent upon the identity of a genus of antigens expressed by cancer cells. The genus of antigens is highly variant because it includes any cancer antigen accessible to an antibody, without limitation as to the structure or function of said antigen. Schlom (Monoclonal Antibodies: They're More and Less Than You Think, In: Molecular Foundations of Oncology, 1991, Ed. S. Broder, pp. 95-134) teaches that a limitation to the potential usefulness of mAb drug or toxin conjugates as effective oncolytic agents is the necessity for the mAb conjugate to internalize for cytotoxic activity (page 107, second column, lines 5-10 under the heading "Drug and Toxin mAb Conjugates"). Schlom teaches that some solid tumor membrane antigens are stable cell surface components and therefore monoclonal antibody conjugates targeted to these antigens will be ineffective (page 107, second column, lines 10-14 under the heading "Drug and Toxin mAb Conjugates"). Chari et al (Cancer Research, 1992, Vol. 52, pp. 127-131) corroborates with the teachings of Schlom, stating that a limitation for achieving sufficient intracellular concentration of drug necessary to kill tumor cells is the inefficient internalization process for antigen/antibody complexes (page 127, first column, second paragraph under "Introduction", lines 9-16). Schlom teaches that this limitation may not apply in cases where the chemical bond utilized to link the drug to the antibody is sufficiently labile to permit disassociation from the antibody at the tumor periphery (page 107, second column, lines 18-25 under the heading "Drug and Toxin mAb Conjugates"). Chari et al teach that the same disulfide linkers which are described in the instant invention are cleaved inside the cell to release active drug (page 127, first column, last paragraph). One of skill in the art would conclude that the conjugates of the instant invention are optimized for cleavage within the cell

rather than cleavage outside of the cell, and that said linkers would be useful only for immunoconjugates which are internalized after binding to the target cancer antigen. The specification describes immunoconjugates comprising monoclonal antibodies which bind to the C56 antigen on cancer cells, as well as the specific monoclonal antibody of N901 which binds to the C56 antigen. The specification also describes the immunoconjugate comprising the C242 antibody which binds to the CanAg on the surface of colorectal cancer cells. The specification describes the cancer antigens of C56 and CanAg. The description of these two species fails to adequately represent the genus of cancer antigens on which the claims depend because the genus of cancer antigens is highly variant encompassing cancer antigens which are integral membrane portion and not internalized, as well as antigens which are inefficiently internalized. It is noted that the claims are drawn to pharmaceutical compositions and kits containing an immunoconjugate comprising a monoclonal antibody which binds to the cancer antigen rather than the cancer antigen itself. However, it flows logically that because the cancer antigens lack adequate written description, the monoclonal antibodies which bind to said antigens also lack adequate written description. One of skill in the art would reasonably conclude that applicant was not in possession of the claimed invention.

As drawn to new matter

Claim 120 is drawn in part to a synergistic combination of taxol and at least one immunoconjugate of maytansinoid conjugated to a monoclonal antibody which binds to an antigen expressed by the cancer cell. the specification and claims as filed provide support only for the combination of huN901-DM1/paclitaxel, or huC242-DM1/paclitaxel for eliciting a synergistic therapeutic effect (examples 2 and 6, pages 33 and 37). Without a specific description of a genus of antibodies which exert a synergistic therapeutic effect when administered with taxol, one of skill in the art would not assume that the generic combination of antibodies with taxol would exhibit a synergistic effect. Claim 120 is therefore rejected for broadening the scope of the invention as originally filed.

7. Claims 93-97, 99, 102-110, 112, 115-119 are rejected under 35 U.S.C. 103(a) as being unpatentable over Siegall et al (Proc Annu Meet Am Assoc Cancer Res, 1997, Vol. 38, page A185) in view of Chari et al (Cancer Research, 1992, Vol. 52, pp. 127-131).

Claim 93 is drawn to a pharmaceutical composition comprising a therapeutically effective amount of at least one chemotherapeutic agent and at least one immunoconjugate; wherein the immunoconjugate comprises at least one maytansinoid compound linked to a monoclonal antibody or fragment thereof and wherein the monoclonal antibody or fragment thereof bind to an antigen expressed by a cancer cell. Claims 94-97 embody the composition of claim 93, wherein the chetoherpae6uic agent is paclitaxel. Claim 99 embodies the composition of claim 93 wherein the monoclonal antibody or fragment thereof is at least one of Fv, Fab, Fab' or F(ab')2. Claims 102-104 specify the structure of a modified maytansinoid having a "thiol handle" for conjugation to an antibody.

Claim 106 is drawn to a kit comprising a therapeutically effective amount of at least one chemotherapeutic agent and at least one immunoconjugate; wherein the immunoconjugate comprises at least one maytansinoid compound linked to a monoclonal antibody or fragment thereof and wherein the monoclonal antibody or fragment thereof bind to an antigen expressed by a cancer cell. Claims 107-110 embody the kit of claim 106 wherein the chemotherapeutic agent is paclitaxel. Claim 112 embodies the kit of claim 106 wherein the monoclonal antibody or fragment thereof is at least one of Fv, Fab, Fab' or F(ab')2. Claims 115-117 specify the structure of the maytansinoid having a "thiol handle" for conjugation to an antibody. Claim 118 and 119 specify that the kit of claim 106 comprises the immunoconjugate and chemotherapeutic agent are in the form of separate compositions, and compositions within the kit, respectively.

Siegall et al teach that combination therapy with BR96 sFv-PE40 and the chemotherapeutic agent paclitaxel were found to have greater antitumor effects in rodents carrying large tumor burdens than either agent alone. The immunotoxin of Siegall et al comprised a single chain antibody which binds to the LeY antigen expressed by human carcinomas, thus fulfilling the specific embodiment of an antibody or fragment thereof that binds to an antigen expressed by a cancer cell, and the specific embodiment of a fragment of a monoclonal antibody that is Fv. Siegall et al teach an immunotoxin conjugated to PE40, which is a modified from of pseudomonas endotoxin . Siegall et al do not teach a BR96 sVf-maytansinoid.

Chari et al teach the chemical synthesis of the structures of claims 102-105, 115-117 and 120. Chari et al teach the conjugation of an antibody which specifically binds to the neu antigen

on tumor cells tumor cells, TA.1 (page 128, first column, lines 17-22, Figure 2, page 129, figure 3). Chari et al teach that the high specific activity of maytansinoid conjugate toward tumor cell lines in comparison with low systemic toxicity indicates that these potent conjugates may possess a therapeutic index sufficient for the effective treatment of human cancer (page 130, first column, lines 5-9). Chari et al teach the advantage of using protein toxins versus anticancer drugs in immunoconjugates lies in the fact that protein toxins act catalytically rather than stoichiometrically (page 127, first column, lines 16-22 under the heading of "Introduction").

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to substitute maytansinoid for the PE40 toxin in the combination of BR96-sFv-PE40 taught by Siegall et all. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Chari et al on the catalytic action of protein toxins versus the stoichiometric action of anticancer drugs. One of skill in the art would recognize that both PE40 and maytansin are protein toxins which would act catalytically within the cell, thus one of skill in the art would expect that a BR96-sFv-maytansinoid immunotoxin would have a similar therapeutic potential as the Br96-sFc-Pe40 immunotoxin.

8. Claims 93-97, 99, 101-110, 112 and 114-119 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liu (Expert Opinion on Investigational Drugs, 1997, Vol. 6, pp. 169-172, cited in a previous Office action) in view of the abstract of Iwasaki et al (Yakugaku Zasshi, 1998, Vol. 118, pp. 111-126) and Pegram et al (Oncogene, 1999, Vol. 18, pp. 2241-2251) and Watson et al (Proc Ammu Meet Am Assoc Cancer Res, 1996, Vol. 37, page A2997) and (Schlom (Monoclonal Antibodies: They're More and Less Than You Think, In: Molecular Foundations of Oncology, 1991, Ed. S. Broder, pp. 95-134). The specific embodiments of claims 93-97, 99, 102-110, 112, 115-119

Claim 101 embodies the pharmaceutical composition of claim 93 wherein the monoclonal antibody or fragment thereof is humanized C242. Claim 114 embodies the kit of claim 106 wherein the monoclonal antibody or fragment thereof is humanized C242.

Liu et al teach a C242-DM1 conjugate (pages 170 to 171 in sections 2 and 3 Liu et al teach that the C242 maytansinoid conjugate killed antigen positive COLO 205 cells in vitro and

caused decreased tumor burden of transplanted human colon cancer xenographs in immunodeficient mice.). Liu et al teach that a reason for lack of clinical efficacy with antibody drug conjugates can be attributed to insufficient accumulation of drug both intratumorally and intracellularly to kill large numbers of tumor cells (page 169, second column, last paragraph). Liu et al teach that this phenomenon can be attributed to the limited expression of target antigens on tumor cells which restricts the amount of drug delivered (page 170, first column, line 8-10) as well as lack of cytotoxic potency and inefficient release of the active drug from the antibody inside the cell (page 170, first column, lines 2-7 and lines 14-15). Liu et al teach that maytansinoids effect cell killing by interfering with the formation of microtubules and depolymerization of already existing microtubules (page 170, column 1, lines 23-26). Liu et al do not teach the administration of the C242-Dm1 conjugate with taxol.

The abstract of Iwasaki et al teaches the existence of a distinct rhizoxin/maytansinoid binding site within tubulin which partially overlaps the vinblastine binding site (VLB). The abstract teaches that taxol binds to tubulin at a site other than the colchicine site (CLC) or the vinblastine site (VLB) and that taxol is an antitubulin agent which promotes microtubule formation (lines 29-32).

Watson et al teaches that taxol stabilizes microtubules resulting in the arrest of the cells at G2/M. One of skill in the art would conclude that taxol was an anti-mitotic agent as cells were arrested at G2/M and unable to go through mitosis and enter G1.

Pegram et al teach that the interaction between two drugs may result in an additive effect, a synergistic effect, or an antagonistic effect. Pegram et al point out that two drugs targeting the same enzyme or biochemical pathway may compete with one another resulting in an antagonistic interaction (page 2242, first column, lines 6-9).

Schlom teaches that in all of the previous reported human trials in which non-immunosuppressed patients were treated with multiple doses of marine antibodies only the first and perhaps the second dose of said antibody was efficiently reaching the tumor site due to the HAMA response. Schlom teaches that it is unrealistic to assume that just one or two administrations of any anti-cancer therapeutic would be effective. Schlom teaches that the answer to this problem is the humanization of the marine antibodies (pages 97-98, bridging paragraph).

Schlom teaches the advantages of single chain antibodies over the parent marine antibodies comprise rapid clearance from the blood and body to avoid unwanted by-stander tissue toxicity, reduced accumulation in the kidneys, especially for the avoidance of renal toxicity associated with drug conjugated antibodies, increased penetration of tumor masses, reduced immunogenicity due to lack of antibody effector domains (page 122, second column, lines 2-23) as well as relative ease of production (lines 27-30). One of skill in the art would be motivated to make the humanized version of the C242 antibody for administration of the maytansinoid immunoconjugate to humans. One of skill in the art would also be motivated to make the scFv fragment of the C242 for administration to humans based on the teachings of Liu et al regarding the poor penetration of immunoconjugates into tumor (page 170, first column, lines 11-12) and the teachings of Schlom on the enhanced ability of scFv to penetrate tumor vasculature and the decreased HAMA response associated with antibody fragments. One of skill in the art would logically be motivated to make a reagent which would maximize the delivery of the maytansinoid to the tumor. By making a humanized C242 antibody, the lack of a HAMA response will allow more of the antibody to reach the tumor on subsequent doses. By making a scFv from C242 the smaller fragment will have a decreased HAMA response and better ability to penetrate into the tumor.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to combine the administration of a humanized C242-DM1 immunoconjugate with taxol or the administration of scFv of C242-DM1 with taxol for the treatment of colorectal tumors. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Liu et al on the limited expression of target antigens on tumor cells which restricts the amount of drug delivered as an impediment to the clinical efficacy of immunoconjugates and the teachings of Liu et al on the antitubulin mode of action of maytansinoid, the delivered drug. One of skill in the art would realize that tumors which are lacking the CanAg to which the C242 antibody binds will not internalize the immunoconjugate and thus will not be exposed to enough anti-tubulin inhibiting drug within the cytoplasm. In addition the teachings of Pegram et al point out that administration of two drugs could result in antagonism if the two drugs were targeted to the same molecular mechanism. The teachings of Liu et al point out that maytansinoids kill cells by

interfering with the formation of microtubules and depolymerization of already existing microtubules. The teachings of the abstract of Iwasaki et al point out that taxol stabilizes microtubulin and does not bind to the same site on tubulin as vinblastine. The teachings of Watson et al point out that taxol arrests cells in G2/M due t the stabilization of microtubulin.

One of skill in the art would be motivated to combine the C242-DM1 immunotoxin with taxol in order to exert a cytotoxic effect on cells which do not express enough of the CanAg targeted by the C242 antibody to result in accumulation of a sufficient amount of the maytansinoid to be cytotoxic. One of skill in the art would recognize that in the cells which express enough of the CanAg to internalize the C242-Dm1 immunoconjugate to the extent that sufficient Maytansinoid will accumulate and exert a cytotoxic effect, taxol will not compete with maytansinoid in the binding of tubulin because taxol and maytansinoid bind to different sites on tubulin, and thus, the administration of taxol in combination with C242-DM1 would not result in an antagonistic effect on said cells. Because the mechanisms of action of these two agents differ with respect to the molecular basis by which they induce an anti-mitotic effect, it is logical to suppose that the combination of the two agents might produce some additive effect.

9. Claims 93-98, 100-111, 113, 115-119 are rejected under 35 U.S.C. 103(a) as being unpatentable over the abstract of Guchelaar et al (Clinical Oncology, 1994, Vol. 6, pp. 40-48) in view of Liu et al (Proc Annu Meet Am Assoc Cancer Res, 1997, Vol. 38, page A190) and the abstract of Lynch et al (Journal of Clinical oncology, 1997, Vol. 15, pp. 723-734) and Liu (Expert Opinion on Investigational Drugs, 1997, Vol. 6, pp. 169-172, cited in a previous Office action) and the abstract of Iwasaki et al (Yakugaku Zasshi, 1998, Vol. 118, pp. 111-126) and Pegram et al (Oncogene, 1999, Vol. 18, pp. 2241-2251). The specific embodiments of claims 93-97, 101-110, 115-119 are set forth above. Claim 98 embodies the composition of claim 93 wherein the monoclonal antibody binds to a CD5 antigen. Claim 100 embodies the composition of claim 93 wherein the antibody or a fragment thereof is humanized N901. Claim 111 embodies the kit of claim 106 wherein the monoclonal antibody or a fragment thereof binds to CD56. Claim 113 embodies the kit of claim 106 wherein the monoclonal antibody or a fragment thereof is humanized N901.

The abstract of Guchelar et al teaches that taxol shows a 37% response rate in the treatment of advanced small cell lung cancer. The abstract does not teach the administration of the humanized N901-DM1 conjugate.

Liu et al (AACR) teach that the administration an immunotoxin conjugate comprising the humanized N901 antibody and maytansinoid (DM1) was effective at killing human small cell lung xenographs in immunodeficient mice. The abstract of Lynch et al teaches that N901 is a monoclonal antibody that binds to the CD56 neural cell adhesion molecule of NCAM., thus fulfilling the specific embodiment of claims 98and 11 specifying binding to CD56. Liu et al do not teach the administration of taxol

The abstract of Watson et al teaches that taxol stabilizes microtubules resulting in the arrest of the cells at G2/M. One of skill in the art would conclude that taxol was an anti-mitotic agent as cells were arrested at G2/M and unable to go through mitosis and enter G1.

The abstract of Iwasaki et al teaches the existence of a distinct rhizoxin/maytansinoid binding site within tubulin which partially overlaps the vinblastine binding site (VLB). The abstract teaches that taxol binds to tubulin at a site other than the vinblastine site (VLB) and that taxol is an antitubulin agent which promotes microtubule formation (lines 29-32).

Liu et al(EOID) teach that maytansinoids kill cells by interfering with the formation of microtubules and depolymerization of already existing microtubules (page 170, first column, lines 2326). Liu et al teach the modified structure of maytansinoid allowing for the attachment of a monoclonal antibody by means of the thiol "handle" (figure1, structure 2).

Pegram et al teach that the interaction between two drugs may result in an additive effect, a synergistic effect, or an antagonistic effect. Pegram et al point out that two drugs targeting the same enzyme or biochemical pathway may compete with one another resulting in an antagonistic interaction (page 2242, first column, lines 6-9).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to combine the administration of a humanized N901-DM1 immunoconjugate with taxol for the treatment of small cell lung carcinoma. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of the abstract of Guchelaar et al who indicate that the administration of taxol alone has some efficacy in the treatment of advanced small cell lung carcinoma; the teachings of Liu et

al (AACR) on the efficacy of the N901-DM1 immunoconjugate against human small cell lung cancer xenographs and the teachings of the abstract of Iwasaki et al and Liu (EOID) on the different binding sites of maytansinoid and taxol on tubulin, and the teachings of Liu (EOID) and the abstract of Watson on the different effects exerted on tubulin by taxol and maytansinoid in light of the teachings of Pergram on the avoidance of targeting the same molecular mechanism by the administration of two drugs wherein the resulting in the effect would be antagonistic. In the instant case the binding of tubulin by taxol would not result in an antagonistic competition with maytansinoid because taxol and maytansinoid bind tubulin at separate locations. Because the mechanisms of action of these two agents differ with respect to the molecular basis by which they induce an anti-mitotic effect, it is logical to suppose that the combination of the two agents might produce some additive effect.

10. Claims 93-113 and 115-119 are rejected under 35 U.S.C. 103(a) as being unpatentable over the abstract of Guchelaar et al Clinical Oncology, 1994, Vol. 6, pp. 40-48) and Liu et al (Proc Annu Meet Am Assoc Cancer Res, 1997, Vol. 38, page A190) and Liu (Expert opinion on Investigational Drugs, 1997, Vol. 6, pp. 169-172 and the abstract of Iwasaki et al (Yakugaku Zasshi, 1998, Vol. 118, pp. 111-126) and Pegram et al (Oncogene, 1999, Vol. 18, pp. 2241-2251) as applied to claims 93-98, 100-111, 113, 115-119 above, and further in view of Schlom (Monoclonal Antibodies: They're More and Less Than You Think, In: Molecular Foundations of Oncology, 1991, Ed. S. Broder, pp. 95-134). The specific embodiments of the claims and the teachings of the combined references which render obvious claims 93-98, 100-111, 113, 115-119 are set forth above. Claim 99 embodies the composition of claim 93 wherein the monoclonal antibody or fragment thereof is at least one of Fv, Fab, Fab' or F(ab')2. Claim 112 embodies the kit of claim 106 wherein the monoclonal antibody or fragment thereof is at least one of Fv, Fab, Fab' or F(ab')2.

None of Guchelaar et al, Liu et al (AACR), Liu et al (EOID), the abstract of Iwasaki et al nor Pegram et al teach the administration of fragments of N901.

Liu et al (EOID) teach that a lack of clinical efficacy of immunoconjugates can be attributed to poor penetration of said immunoconjugates into tumors (page 170, first column, lines 11-12).

Schlom teaches the advantages of single chain antibodies over the parent murine antibodies comprise rapid clearance from the blood and body to avoid unwanted by-stander tissue toxicity, reduced accumulation in the kidneys, especially for the avoidance of renal toxicity associated with drug conjugated antibodies, and increased penetration into tumor masses, (page 122, second column, lines 2-23) as well as relative ease of production (lines 27-30).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to combine taxol with scFv conjugated to DM1 in place of N901-DM1. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Liu et al regarding the lack of tumor penetration as a reasons for reduced toxicity of immunoconjugates in vivo, and the teachings of Schlom et al regarding the administration of scFv in place of whole antibodies for increasing tumor penetration in vivo.

11. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentable distinct from the

reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g. In re Berg, 140 F. 3d 1428, 46 USPQ2d 1226 (Fed Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).

12. Claims 93-97, 99, 102-110, 112, 115-119 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-12 of U.S. Patent No. 5,208,020 in view of Siegall et al (Proc Annu Meet Am Assoc Cancer Res, 1997, Vol. 38, page A185) and Chari et al (Cancer Research, 1992, Vol. 52, pp. 127-131).

The specific embodiments of the claims are set forth above.

Siegall et al teach that combination therapy with BR96 sFv-PE40 and the chemotherapeutic agent paclitaxel were found to have greater antitumor effects in rodents carrying large tumor burdens than either agent alone. The immunotoxin of Siegall et al comprised a single chain antibody which binds to the LeY antigen expressed by human carcinomas, thus fulfilling the specific embodiment of an antibody or fragment thereof that binds to an antigen expressed by a cancer cell, and the specific embodiment of a fragment of a monoclonal antibody that is Fv. Siegall et al teach an immunotoxin conjugated to PE40, which is a modified from of pseudomonas endotoxin . Siegall et al do not teach a BR96 sVf-maytansinoid.

Chari et al (Cancer Research) teach the advantage of using protein toxins versus anticancer drugs in immunoconjugates lies in the fact that protein toxins act catalytically rather than stoichiometrically (page 127, first column, lines 16-22 under the heading of "Introduction").

Claims 1-6 of the '020 patent are drawn in part to cytotoxic agents comprising one or more maytansinoids conjugated to a monoclonal antibody or fragment thereof via a disulfide bridge at the C3 position of said maytansinoids and wherein said monoclonal antibody or fragment thereof is selective for tumor cell antigens. Claims 7-12 are drawn to pharmaceutical composition comprising maytansinoids conjugated to a monoclonal antibody or fragment thereof via a disulfide bridge at the C3 position of said maytansinoids and wherein said monoclonal antibody or fragment thereof is selective for tumor cell antigens. Conjugation of the monoclonal antibody to the maytansinoid via the C3 position of maytansinoid is the same as the structures of instant claims 102,-105 and 115-117.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to substitute maytansinoid for the PE40 toxin in the combination of BR96-sFv-PE40 taught by Siegall et all. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Chari et al (Cancer Research) on the catalytic action of protein toxins versus the stoichiometric action of anticancer drugs. One of skill in the art would recognize that both PE40 and maytansin are protein toxins which would act catalytically within the cell, thus one of skill in the art would expect that a BR96-sFv-maytansinoid immunotoxin would have a similar therapeutic potential as the Br96-sFc-Pe40 immunotoxin.

Thus, the instant claims 93-97, 99, 102-110, 112, 115-119 would have been obvious over, the reference claim(s) 1-12 because it would be obvious to combine the reference claims with the teachings to Siegall et al and Chari et al (Cancer Research) for the reasons set forth above.

Applicant argues that after a reading of Liu et al on the administration of C242-DM1 one of skill in the art would be motivated to use the immunoconjugate as a single agent and thus the disclosure of Liu et al actually teaches away from the instant invention. This has been considered but not found persuasive. the teachings of Liu et al are directed to the decrease in tumor burden of a human xenograph in immunodeficient mice. Liu et al teaches that some of the reasons why clinical efficacy has not been realized for immunoconjugates is due to the lack of expression of the target antigen on the tumor cell and the lack of penetration of the targeting antibody into the tumor mass both of which would result in lack of accumulation of the toxin within the targeted tumor cells. The experiment with transplanted tumor in mice involve the transplantation of tumor cell lines. Tumors growth in situ differ from tumor cell lines in three dimensional organization and in molecular heterogeneity. Schlom (cited above) teaches the parameters for monoclonal antibody based therapy which include number of antigen molecules per cell, number of cells expressing the reactive antigen in the tumor mass, the size and degree of vascularization of the tumor mass (page 98, Table 6.2). Schlom also teaches that "virtually every property of a tumor cell population has been shown to demonstrate some degree of heterogeneity or modulation either between different tumor masses or among cells of a given tumor mass...expression of some tumor associated antigens is no exception" (page 109, second column, lines 1-10 under the heading "Up Regulation of Target Antigens"). Thus, given the teachings of

Liu et al regarding the lack of clinical efficacy for immunoconjugates due to the lack of effective delivery of the conjugated toxin to a large number of tumor cells one of skill in the art would not expect, based on a transplanted tumor animal model, that the C242-DM1 would be effective as a single agent for the treatment of colorectal cancers because the transplanted xenograph is a transplanted tumor cell line which differs from a tumor in situ in that a tumor in situ is expected to exhibit antigen heterogeneity as taught by Schlom and Liu et al.

13. All other rejections and objections as set forth in the previous Office action are withdrawn.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (571) 272-0828. The examiner can normally be reached on Monday through Friday from 9 am to 6:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached on (571) 272-0871. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

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1/24/04